X THE ENDOCRINE SYSTEM

FULLER ALBRIGHT

The investigative work of Fuller Albright concerned primarily the parathyroid glands, metabolic bone disease, and the relations of the pituitary, adrenal, and gonadal glands. Considered the father of clinical endocrinology, Albright combined beautifully a career of precise laboratory investigation and skilled patient care.

Born to distinguished parents in Buffalo, New York, in 1900, Albright attended a school founded by his father and graduated from Harvard College in 1920 and Harvard Medical School in 1924. His senior thesis, "The Physiology and Physiological Pathology of Calcium," was a paper he later described as the worst he ever wrote. After an internship at Massachusetts General Hospital, Albright spent a year in research there, and then a year at Johns Hopkins Hospital, where he befriended Read Ellsworth, with whom he would collaborate on many studies. John Eager Howard (1981) recalled his first association with these men:

> *For some reason Ellsworth and Albright accepted me, then a fourth-year medical student, as their workhorse, and a more strenuous pair of masters never existed. I was assigned all sorts of menial tasks, but especially I recall most vividly having to get up in the middle of the night to attend the first patient diagnosed as having idiopathic hypoparathyroidism.*

Albright then spent a year in Vienna with the pathologist Jacob Erdheim, of whom he later commented, "I will simply state that he knew more about disease processes than any other living man" (Axelrod, 1970). Albright returned to

Massachusetts General Hospital where he remained in practice, teaching, and research.

Author of 118 medical papers and a book entitled *The Parathyroid Glands and Metabolic Bone Disease,* published in 1948, Albright's contributions to endocrinology included descriptions of (1) idiopathic hypoparathyroidism; (2) secondary hyperparathyroidism; (3) diffuse hyperplasia of the parathyroid glands; (4) the relation of renal stones to hyperparathyroidism, coining the term "nephrocalcinosis"; (5) the importance of measuring serum protein levels to estimate bound calcium; (6) a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females," known as Albright's syndrome; (7) rickets resistant to vitamin D therapy; (8) the pharmacodynamic effects of vitamin D; (9) nephrocalcinosis with rickets and dwarfism; (10) the pathogenesis of renal tubular acidosis; (11) hypercalcemia with osteoporosis of disuse; (12) postmenopausal osteoporosis; (13) estrogen treatment of osteoporosis in postmenopausal women; (14) pseudohypoparathyroidism; (15) familial hypoparathyroidism with moniliasis; (16) the danger of immobilization in Paget's disease; (17) the milk-alkali syndrome; (18) pseudopseudohyperparathyroidism; (19) idiopathic hypercalciuria; and (20) a categorization of pituitary-gonadal dysfunction based on measurement of urinary gonadotropins. Albright delivered the 1943 Harvey Lecture in which he distinguished the pathogenesis of Cushing's syndrome and the androgenital syndrome.

Albright was a strong advocate of clinical investigation. His ideas on the subject were published in an article entitled "Some of the 'Do's' and 'Do-Not's' of Clinical Investigation" (Albright, 1944). Of financial support, Albright wrote, "The man and not the project should be endowed." Of medical hypotheses, he thought "any theory is better than none at all," although every theory was subject to change. He utilized arrow-laden diagrams to illustrate many of his points in papers. Of administrative work, which he detested, he wrote, "The desk of a good executive should be clear; that of an investigator should be littered," and he advised that one reserve time each day to think: "If you salvage a few minutes, you will be doing better than most." Albright concluded one paper on osteoporosis with the following statements:

"I have told you more about osteoporosis than I know."

"What I have told you is subject to change without notice."

"I hope I have raised more questions than I have given answers."

"In any case, as usual, a lot more work is necessary."

Albright enjoyed trout fishing in the Adirondack Mountains and bridge with his friends in Boston. He traveled a great deal with his wife and was fond of wearing a tweed jacket, baggy trousers, and a bow tie. He never discussed personalities. He valued integrity and was openly contemptuous of mediocrity in medicine.

But the life of Albright was not without tragedy. At the early age of 36, the tremor of Parkinson's disease appeared, followed by increasingly worse manifestations over the next two decades. His wife was of invaluable support as his dependence on her increased. Members of his profession also came to his aid:

At the M.G.H. his friends did what was necessary. If a shoelace became untied, the nearest person tied it. When he entered the cafeteria, someone would pick up a tray for

him and pay for his meal with the money his wife had stuffed into his pocket that morning. The medical student in Albright's one-month elective course would be given the family's second car, if he did not have his own, and was expected to drive his instructor to and from work, write his notes, and hold his stethoscope against the patient's chest. (Axelrod, 1970)

He rarely mentioned his disease, the severity of which prompted him to insist on surgical intervention at age 56. After initial improvement, a complication occurred that left him an invalid in a state of akinetic mutism for 13 years until his death in 1969. With characteristic humor, at age 46, Albright had written that Parkinson's syndrome "does not come under my special medical interests, or else I am sure I would have it solved long ago" (Howard, 1981).

—CHARLES STEWART ROBERTS

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134 An Overview of the Endocrine System

VICTOR SILVERMAN

Endocrinology provides an exciting and challenging opportunity to the examining clinician. Unlike other internal medicine subspecialties, the physician is not dealing with only one anatomic site or organ. Most endocrine disorders do not present as a single visible or palpable abnormality. With the exception of the thyroid and the testicles, the glands cannot be felt. Physical diagnoses rely on astute observations by the examiner, who, after a careful history, has some clue as to the diagnosis. Endocrine diagnosis involves the sequence of history, physical examination, laboratory, and radiologic evaluation. Over the past two decades less emphasis has been placed on the history and physical while relying more heavily on the laboratory evaluation. In this era of cost containment, however, we are encouraged to rely more on clinical judgment. The endocrinologist must apply cognitive skills based on what he or she hears, sees, and feels. Using these data, the appropriate laboratory testing can be performed to complete the evaluation.

History

Regardless of whether there is an obvious problem, treat each patient as an unknown in order to avoid missing an endocrine disorder. A patient with one endocrine disease (e.g., Hashimoto's thyroiditis) is at greater risk for the development of other endocrine disorders (e.g., adrenal, testicular, or ovarian failure). A patient may harbor more than one endocrinopathy, which could be overlooked if subtle historical and clinical clues are not heeded.

Always allow patients to express themselves. Ask patients how they feel and let them answer. Often, within the first few minutes of the history an endocrine cause becomes apparent. I find it most useful to review the patient's complaints literally from head to toe. The patient's vocal pitch may give a clue. A hypogonadal male has a high-pitched voice, while an androgenized female may have a deeper voice than expected. Body fat distribution gives important clues to the presence of adrenal steroid excess, while excessive wasting may imply adrenal steroid insufficiency or hyperthyroidism. A eunuchoid habitus suggests hypogonadism. Observation of skin color, pattern of wrinkling, distribution of skin pigment, and body hair can yield useful historical clues.

Hair growth is an important piece of information. Ask the patient how often he shaves, and if the frequency has decreased. In the adult male the presence or absence of facial hair and the frequency of shaving give important information as to gonadal status; for example, hypogonadal males with primary (Klinefelter's or Kallman's syndrome) or secondary gonadal insufficiency (atrophic testicles following trauma, mumps, autoimmune diseases, etc.). Family history can be a clue because many families display sparse facial hair growth. Females may complain of excessive body hair, which should lead you to investigate causes of excessive androgens.

The pituitary gland should be investigated through history, physical, and radiographs. If you think of the hormones secreted by the pituitary, appropriate questions can be asked. Adrenocorticotrophic hormone (ACTH) controls glucocorticoid production. Excess ACTH produces the classic Cushing's appearance. Mental changes, fatigue, muscle weakness, easy bruising, infections, stretch marks, and acne are but a few of the findings related to steroid excess. Deficiency of these hormones can produce complaints ranging from fatigue and apathy to dizziness, shock, coma, unexplained fever, joint and abdominal complaints. These findings, coupled with hyperpigmentation, would lead one to suspect primary hypoadrenalism. The absence of hyperpigmentation would lead one to suspect a primary ACTH deficiency. Chapter 144 outlines the tests of endocrine function and demonstrates how one can relate the above findings to the laboratory.

Follicle stimulating hormone (FSH) and luteinizing hormone (LH), also reviewed in Chapter 144, control testicular and ovarian steroid synthesis. In the female, the appropriate sequence of adenarche, thelarche, and menarche should be obtained. Amenorrhea is an important clue in a breakdown in the hypothalamic–pituitary–ovarian axis.

Male sexual development and function require a normal hypothalamic-testicular axis. The history helps assure adequacy of FSH, LH, and testosterone. Certainly a male with a full beard who has fathered children recently does not have a primary hypogonadal process. The presence of normal erections, adequate libido, and a full beard with a normal male body habitus helps exclude hypogonadism without the need for extensive testing.

Growth hormone plays little role in the adult when it is deficient. Growth hormone excess produces acromegaly. History often reveals enlargement of acral parts, tightly fitting rings on the fingers, and an increase in shoe and hat size. Photographs will often demonstrate marked changes in appearance over the years.

Prolactin can produce galactorrhea in the female patient. Any woman who complains of breast secretions deserves an evaluation. The presence of menstrual periods with galactorrhea often implies a benign etiology, while amenorrhea–galactorrhea with elevated prolactin suggests a pituitary tumor.

Thyroid disease also displays protean presenting manifestations. Thyroid dysfunction can be so mild as to be unnoticed by the patient or examiner. Local effects of thyroid gland enlargement may produce only a goiter. Pain and compression of the surrounding structures can occur, however.

Hyperthyroidism in the elderly may cause few complaints other than lassitude, fatigue, weight loss, and constipation. Younger patients often complain of overactivity, nervousness, jitterness, tremulousness, intolerance to extremes in heat, difficulty concentrating, and insomnia. These symptoms may develop so insidiously that the patient does not recognize them until they are specifically quizzed.

Hypothyroidism may present as loss of interest, depression, fatigue, cool dry skin, constipation, mild degree of weight gain, or simply difficulty losing weight. The disorder can progress to the point of extreme and overwhelming hypothermia, coma, and death. The presence of an enlarged thyroid gland is useful in assessing both hyperthyroidism and hypothyroidism. Neck pain, tenderness, and trouble swallowing are important clues to the cause of an enlarged thyroid gland. Severe tenderness heralded by an antecedent viral illness should lead the clinician to think of thyroiditis. Chapter 135 outlines in more detail the history and physical examination of the thyroid gland.

Diabetes (Chapter 136) often presents insidiously with the gradual onset of excessive thirst, urination, nocturnal frequency, weight loss, and increased appetite. These manifestations occur frequently in type II, or non-insulin-requiring adult-onset, diabetes. The more acute development of these symptoms occurs in the type I, or insulin-requiring, diabetes. Blurring of vision, frequent infections, numb or painful extremities, and nonhealing extremity ulcers are important clues that should lead to a diabetic evaluation. Chapters 139 through 141 outline the approach in detail. Careful questioning can be helpful in pinpointing the onset of illness based upon clinical clues.

Chapter 137 describes the importance of observing the patient's physique and build. Extremely short stature with failure to undergo a pubertal growth spurt are clues of growth hormone deficiency. Hypothyroidism plus other hormone deficits often coexist. Individuals who are disproportionately tall in relation to their parents and siblings with complaints of sexual difficulties and gynecomastia may have Klinefelter's or another form of gonadal disturbance. A eunuchoid or female habitus helps in making this assessment.

The symptoms of diabetes mellitus (Chapter 136) may be those of a fulminant illness characterized by extreme thirst, blurring of vision, and nocturia. This presentation is more common for a type I, or insulin-requiring, diabetic as opposed to the insidious complaints of a type II diabetic. Less commonly, the patient may present with complaints of end organ damage. Swelling of the feet secondary to urinary protein loss or renal insufficiency, neuropathic complaints as numbness of the feet or hands, pain in an extremity or in a dermatomal distribution of the body may occur together or separately. A vascular event such as leg cramps on walking (claudication), ulcers of the extremities, or more dramatically stroke and coronary disease may be the initial finding.

Physical Examination

As discussed in the previous paragraphs, the manifestations of endocrine illnesses are so far reaching as to affect almost every organ system. A comprehensive physical examination to complement a complete history is mandatory. Begin with the scalp and progress downward. The necessary instruments are noted in Table 134.1.

Table 134.1
Instruments Used in the Endocrine Examination

Ophthalmoscope
Exophthalmometer
Stethoscope
Percussion hammer
Tuning fork—128 Hz
Blood pressure cuff

With the patient undressed, observe the body size and habitus (Chapter 137). The distribution of body fat may reveal information as to nutrition, thyroid and adrenal status, important clues as to the presence of Cushing's disease. The combination of supraclavicular fullness, moon facies, violaceous striae, dorsal cervical fat pad, and a centripetal truncal obesity is often diagnostic. The penguinoid habitus of the Klinefelter's patient is often recognized at first glance.

Scalp and facial hair as well as the balding pattern are useful clues in assessing the patient's gonadal status. Decreased quantities of facial hair, perioral and periorbital wrinkling may be subtle signs of hypogonadism. In the female, excessive hair, acne, male-pattern balding, and central scalp hair loss are signs of androgen excess.

The presence of retinal changes characteristic of diabetes range from subtle vascular anomalies to microaneurysms, hemorrhages, exudates, retinal buckling or detachment, and proliferative changes. Optic atrophy manifested by disk pallor suggests a pituitary tumor and mandates careful visual field examination. Graves' disease displays classic eye findings. Hyperthyroid eyes may range from redness to protrusion with extraocular muscle and optic nerve dysfunction.

The thyroid gland (Chapter 138) is both visible and palpable. The skilled examiner can often visualize a thyroid nodule or outline a diffusely enlarged gland. The palpable characteristics of the gland may differentiate multinodular goiter, Hashimoto's thyroiditis, nontoxic goiter, and Graves' disease. The thyroid's morphology coupled with the clinical finding of thyroid disease often suggests a diagnosis prior to the return of laboratory tests.

The presence of galactorrhea should lead one to assess for other pituitary disturbances. Gynecomastia in the male may have important clinical significance ranging from hypogonadism to malignancy.

In the male, the genital examination together with peripheral manifestations of gonadal disease may be of high diagnostic yield. One should carefully inspect for the presence of testicles within the scrotum and palpate for size and consistency. In both the male and female, pubic hair patterns are important. Examination of the perineum may yield important information as clitoromegaly or other labial or urogenital abnormalities are noted.

Careful inspection of the hands and feet, especially in diabetics, is important. Diabetic cheiropathy with classic periarticular tightening suggests the presence of vascular disease in other organs and portends a high risk for heart disease. Shiny thin skin with absence of hair on the lower extremities and absent pulses in the feet suggest the presence of macrovascular or microvascular disease of diabetes mellitus.

Examination of the neuromuscular system is of equal importance. The absence of ankle jerks, vibratory sensation, pinprick or light touch, abnormalities in joint position sense, and muscle atrophy in a diabetic indicates diabetic neuropathy.

Proximal muscle weakness is common to other endocrine disorders, such as hyperthyroidism and Cushing's disease.

Conclusion

The entire endocrine history and physical examination can be performed over a 30- to 45-minute period. In many cases, diagnosis with reasonable assurance is made before the patient leaves the examining room.